读书报告

汇报人：职韶阳

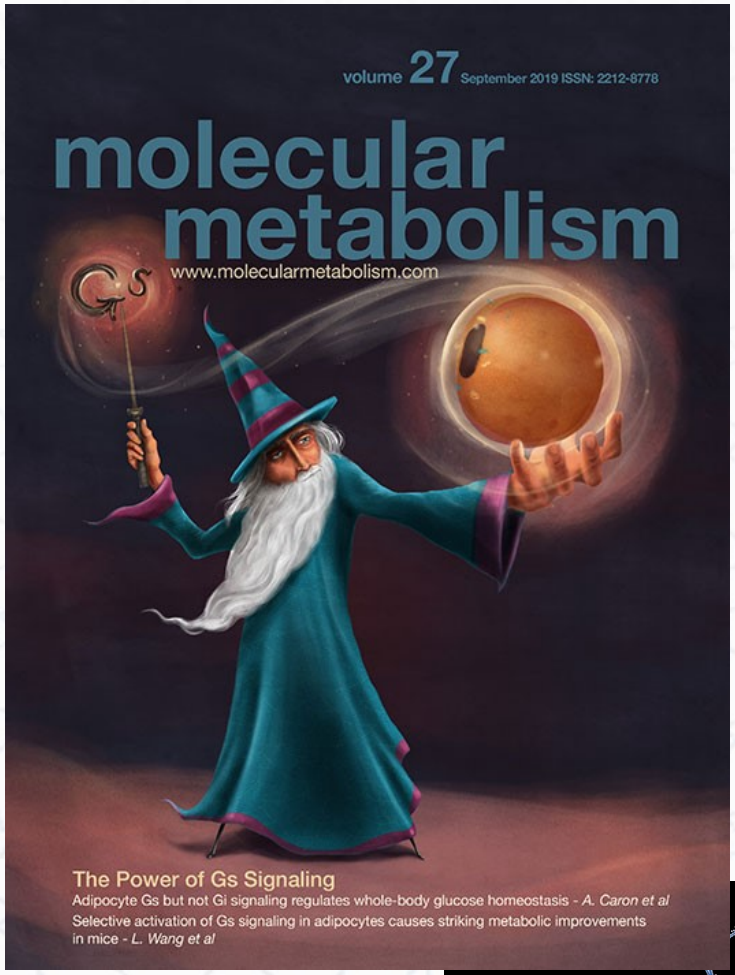
时间：2019年12月15日

MOLECULAR METABOLISM

IF=6.181

E2F1 promotes hepatic gluconeogenesis and contributes to hyperglycemia during diabetes

E2F1促进肝糖异生，并导致糖尿病期间的高血糖症



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研究背景

E2F1：Cell cycle regulatory proteins

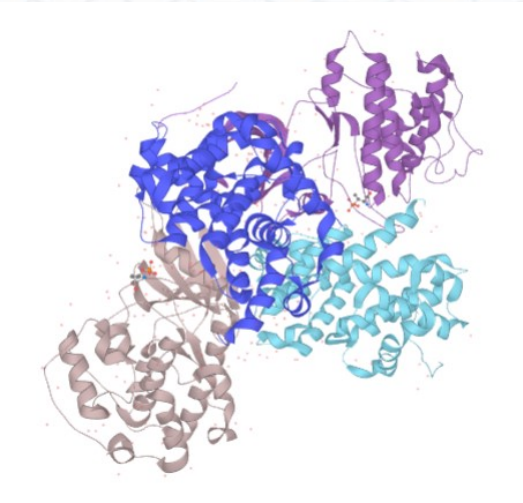
The transcription factor E2F1 is a central player involved in cell cycle progression, DNA-damage response, and apoptosis.（1）

The E2F transcription factors were first identified as proteins that were able to bind to the promoter of the adenoviral gene E2.（2）

Aberrant hepatic glucose production contributes to the development of hyperglycemia and is a hallmark of type 2 diabetes.（4）

E2F1, contributes to hepatic steatosis through the transcriptional regulation of key lipogenic enzymes.（5）

Genome-wide location studies have revealed that E2F1 binds to hundreds of promoter regions of genes involved in a myriad of cellular pathways.（3）



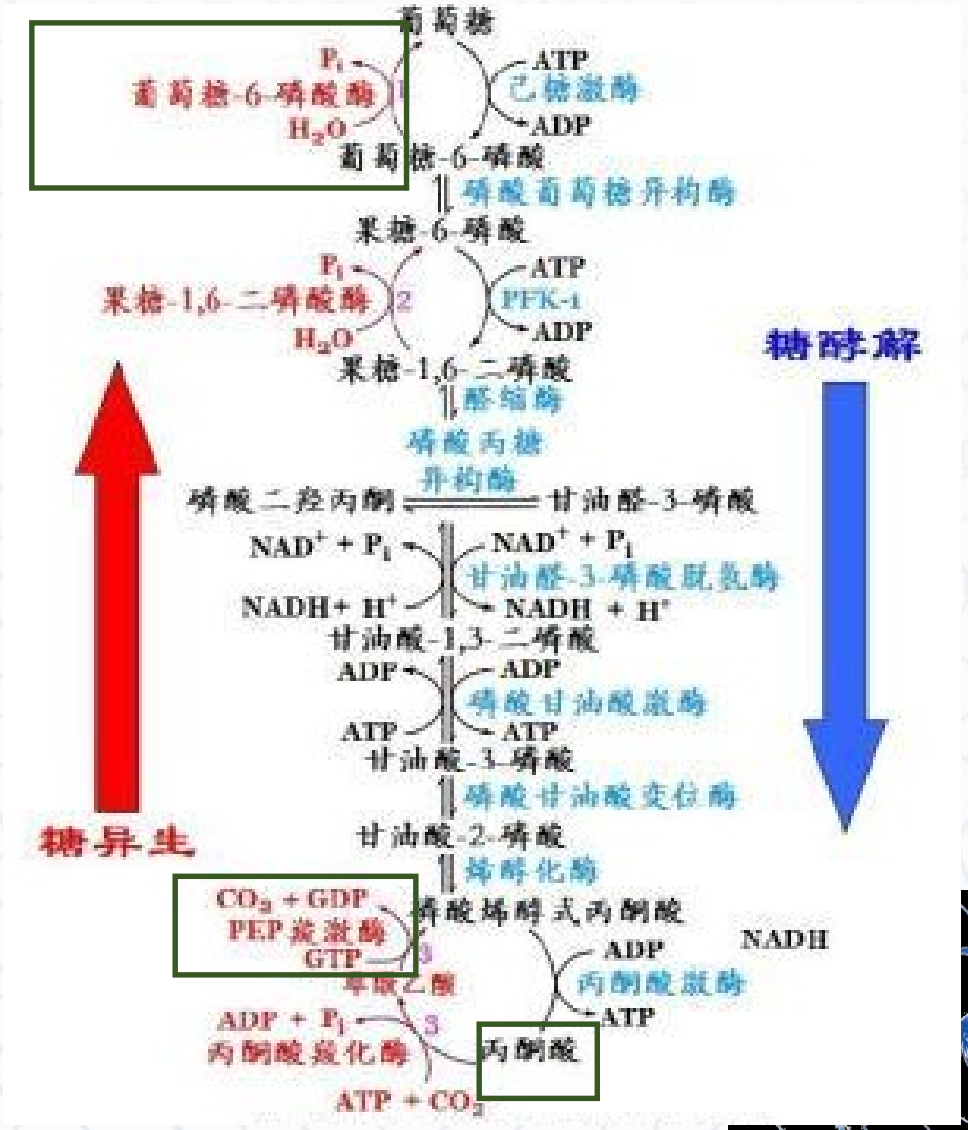
Blood glucose

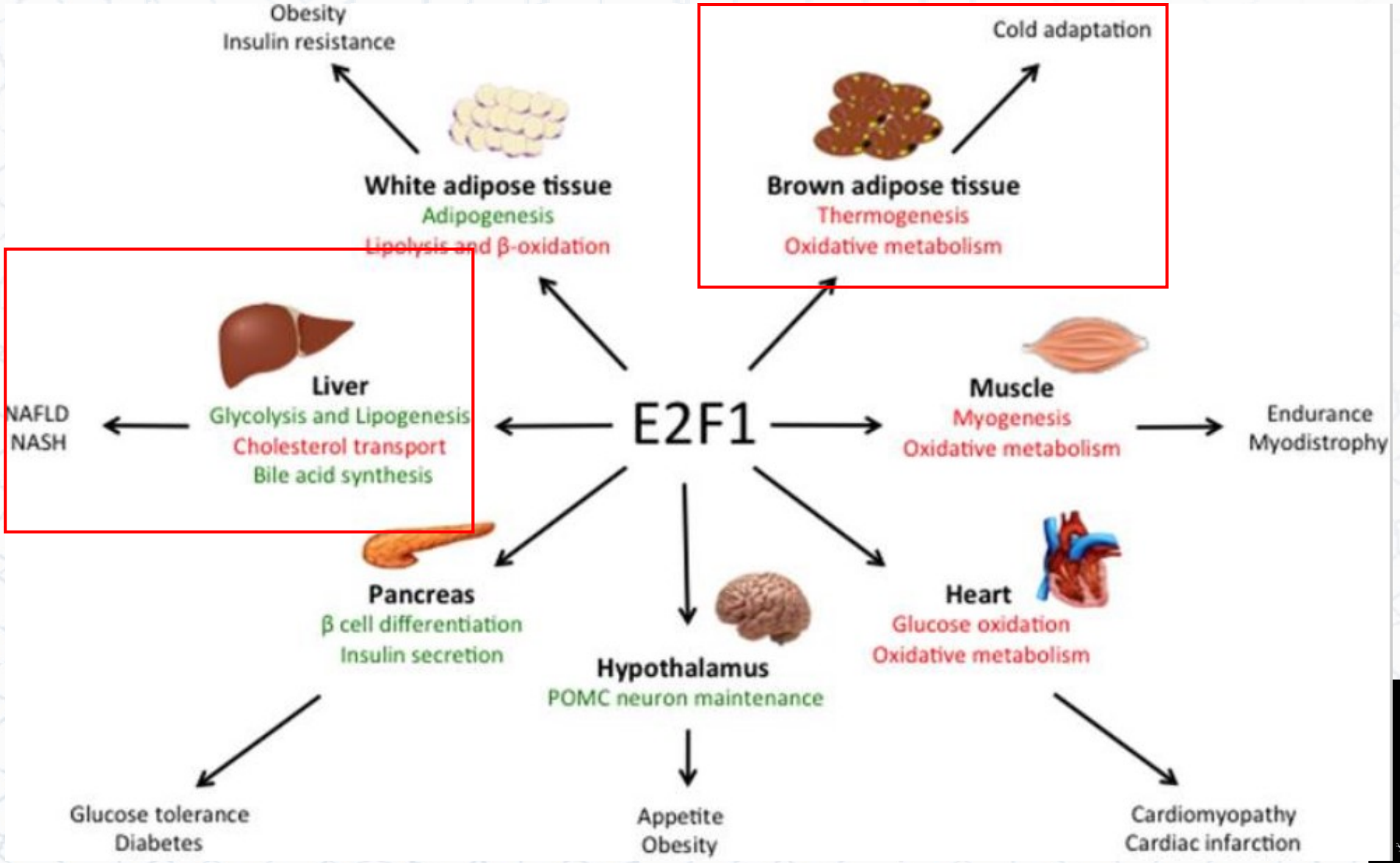
Sustaining blood glucose levels:
Through a complex balance between glucose production and utilization by different tissues.

These processes are dynamically regulated by hormonal and nutritional signals.

Hepatic glucose production, which comprises glycogenolysis and gluconeogenesis.

PCK1 **G6PC**




Obesity
Insulin resistance
White adipose tissue
Adipogenesis
Lipolysis and β-oxidation
Cold adaptation
Brown adipose tissue
Thermogenesis
Oxidative metabolism
NAFLD
NASH
Liver
Glycolysis and Lipogenesis
Cholesterol transport
Bile acid synthesis
E2F1
Muscle
Myogenesis
Oxidative metabolism
Endurance
Myodistrophy
Pancreas
β cell differentiation
Insulin secretion
Hypothalamus
POMC neuron maintenance
Heart
Glucose oxidation
Oxidative metabolism
Glucose tolerance
Diabetes
Appetite
Obesity
Cardiomyopathy
Cardiac infarction

作者提出问题：

E2F1是否通过调节肝糖异生而导致高血糖症。

E2F1是通过什么途径导致此变化。

我的问题：

作者通过什么手段印证了E2F1调节肝糖异生？

如何研究以及印证E2F1及其信号通路。

材料与方法

材料与方法

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1、动物实验

2、细胞培养

3、染色质免疫沉淀

4、Western blot

5、人体样本实验

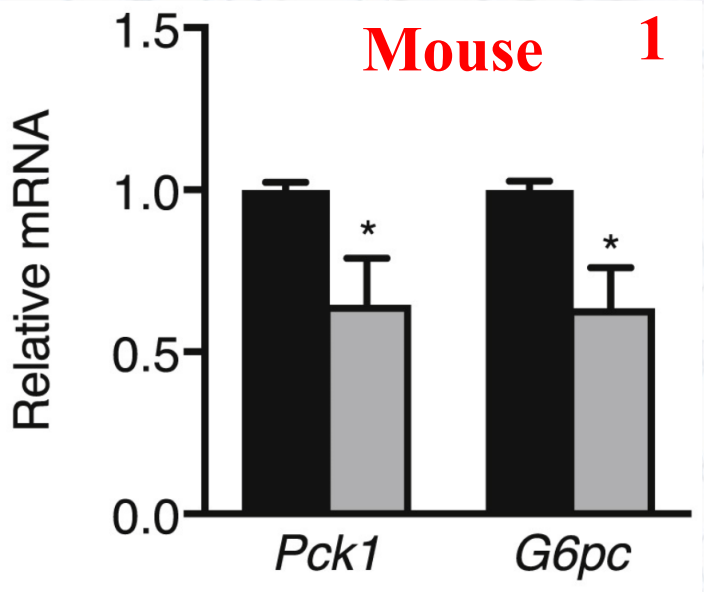
建立过表达、基因敲除模型，评估E2F1的影响

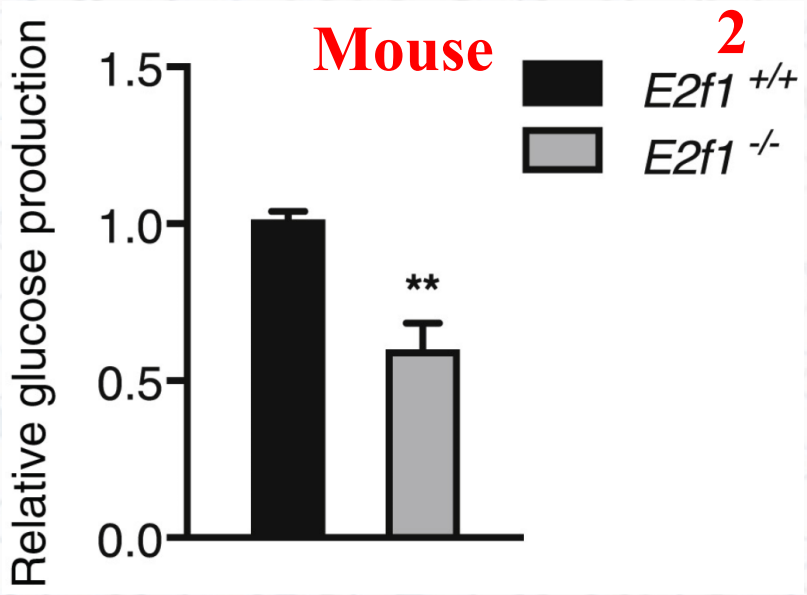
使用不同的遗传模型，探究是否E2F1调节原代肝细胞的糖异生

分析糖尿病患者肝脏中E2F1的mRNA水平，回到人类水平印证结果。

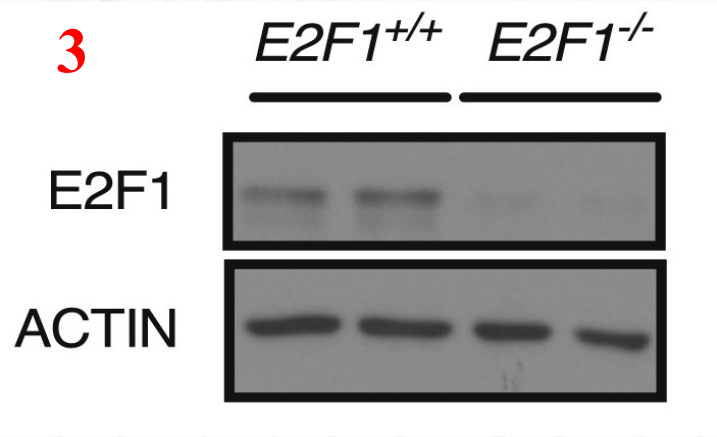
结果与讨论

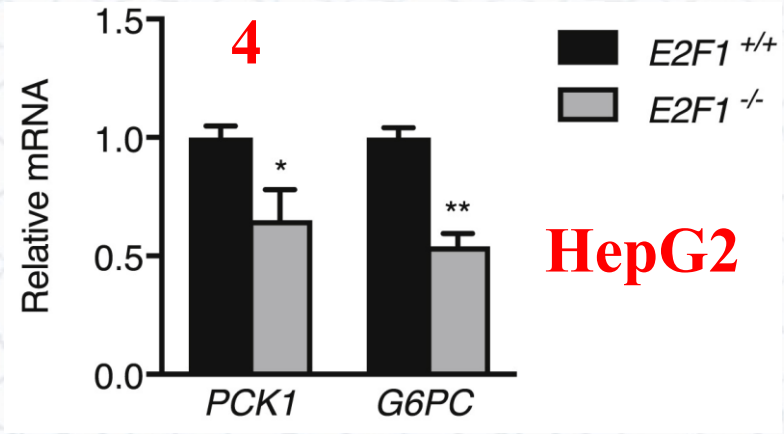
3.1 Lack of E2F1 blunts hepatic gluconeogenesis in hepatocytes





HepG2



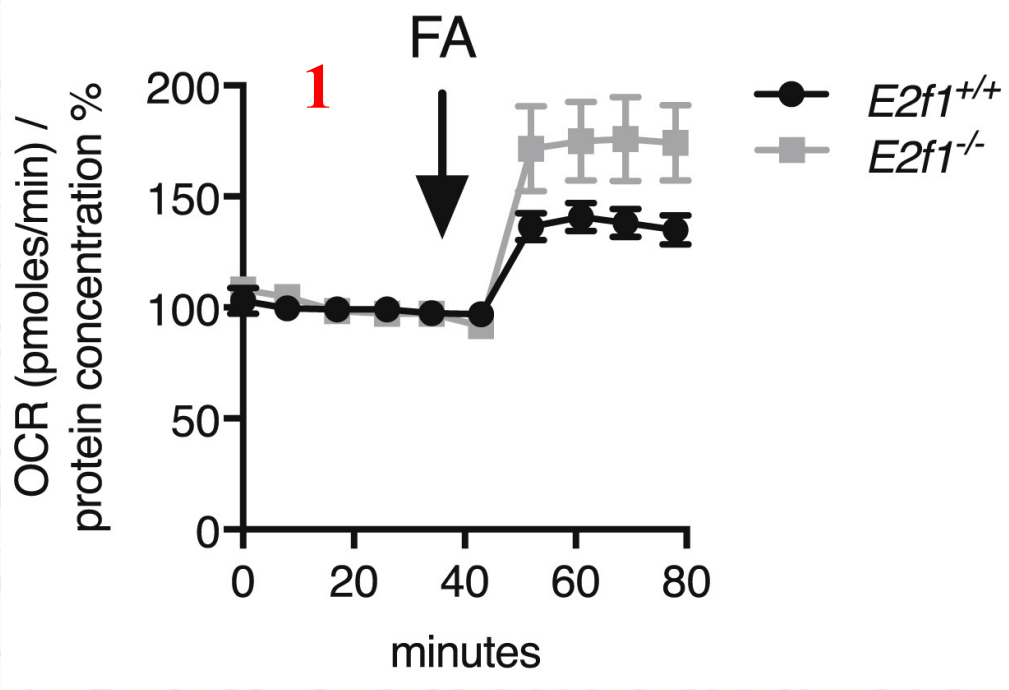


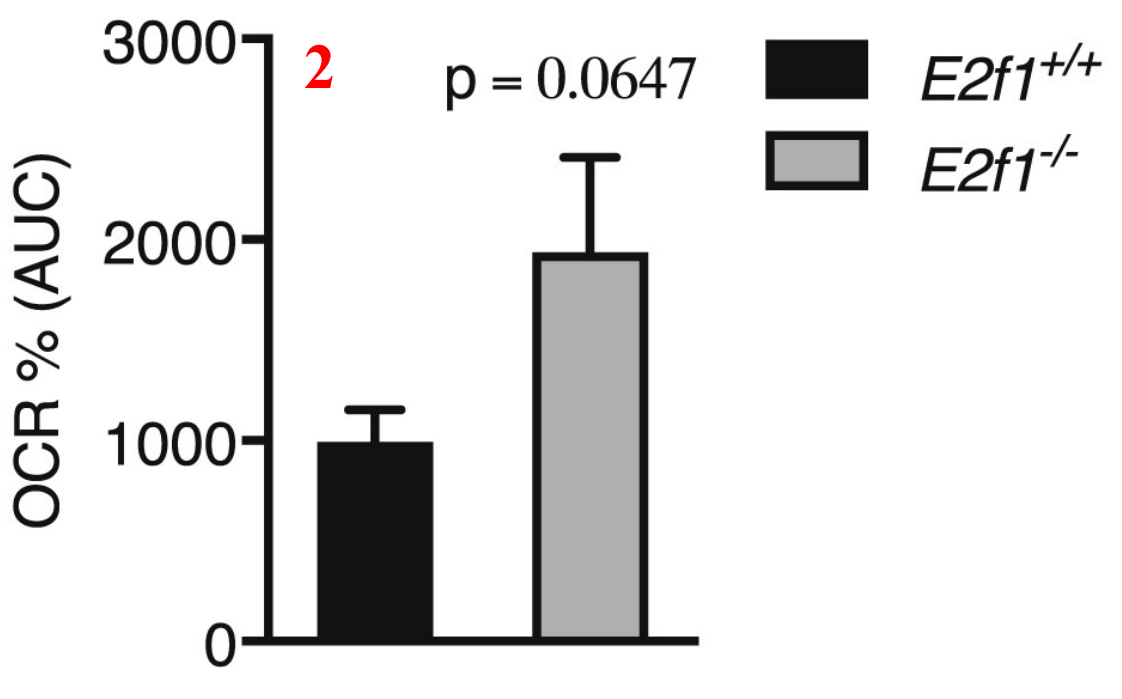
HepG2

3.1 Lack of E2F1 blunts hepatic gluconeogenesis in hepatocytes

原代肝细胞脂肪酸氧化

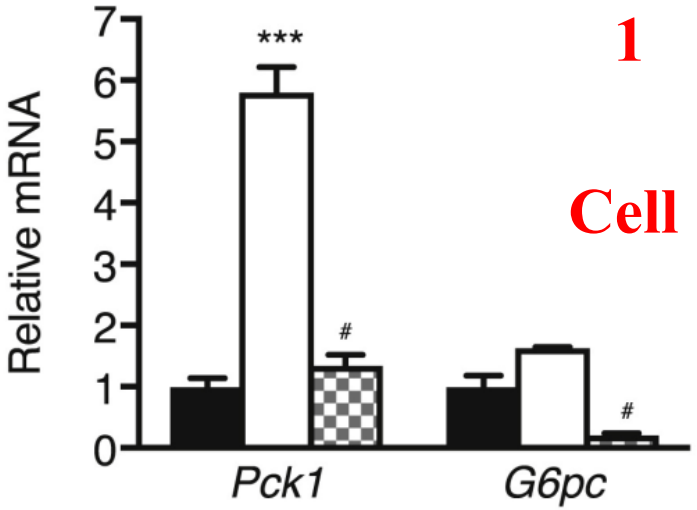
棕榈酸酯诱导

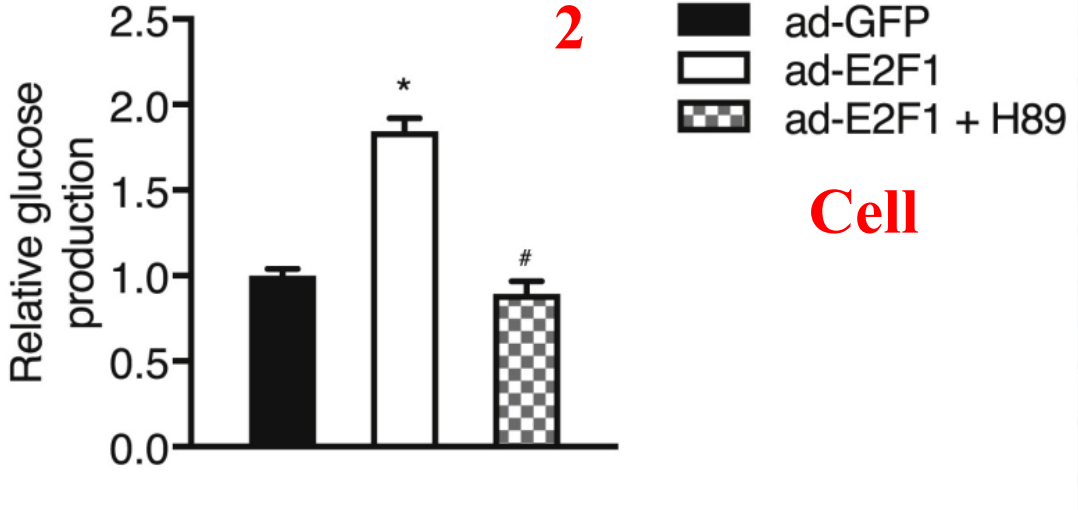


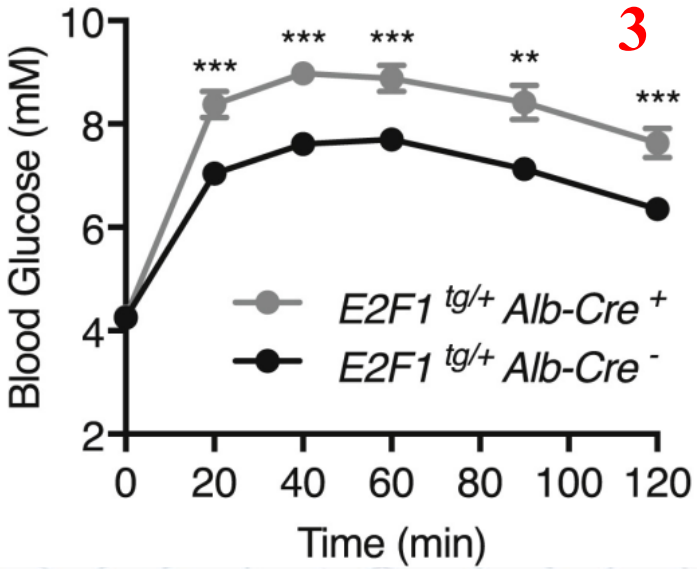


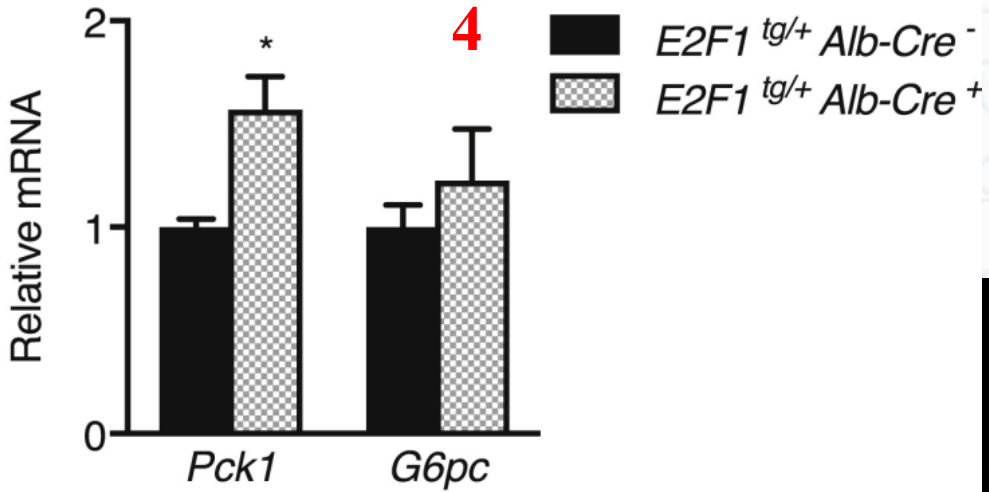
是否在E2F1敲除的肝细胞中，观察到的糖异生基因的变化是由于线粒体功能受损引起的？

3.2 Overexpression of E2F1 induces gluconeogenesis in primary hepatocytes and in liver









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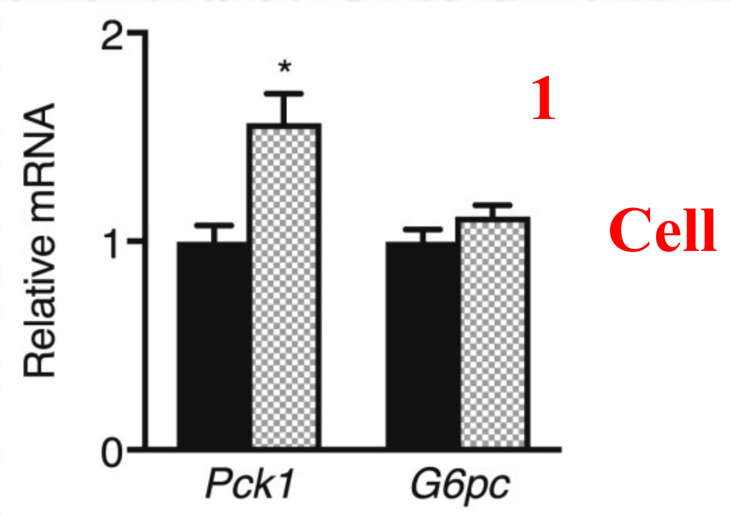
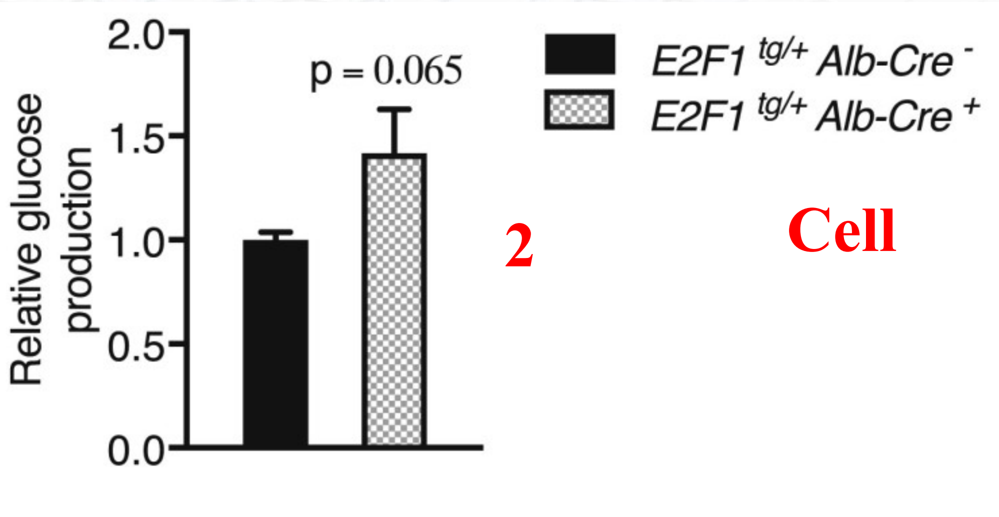
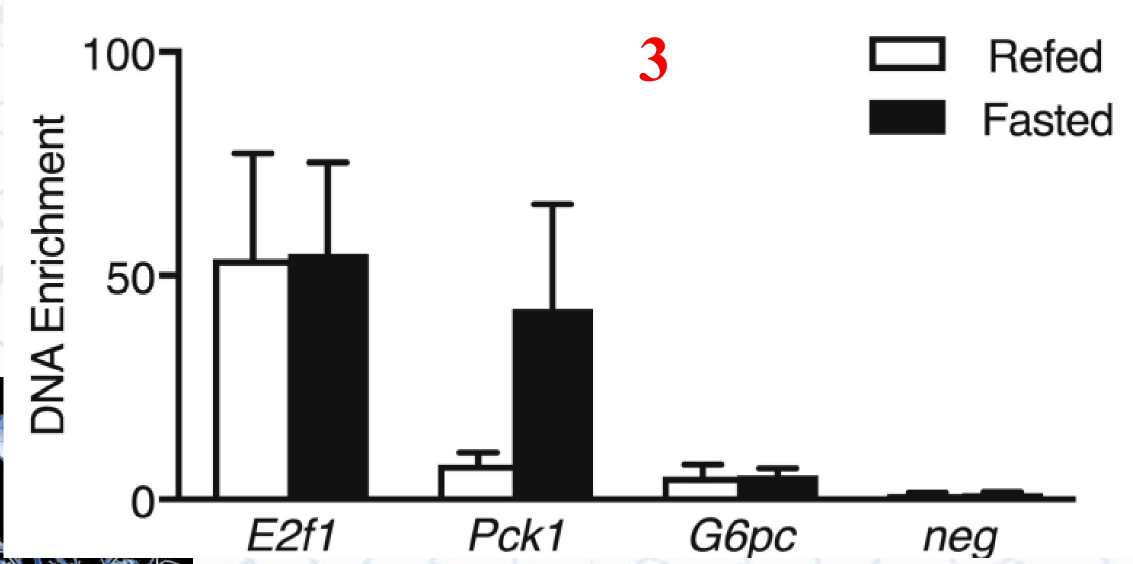


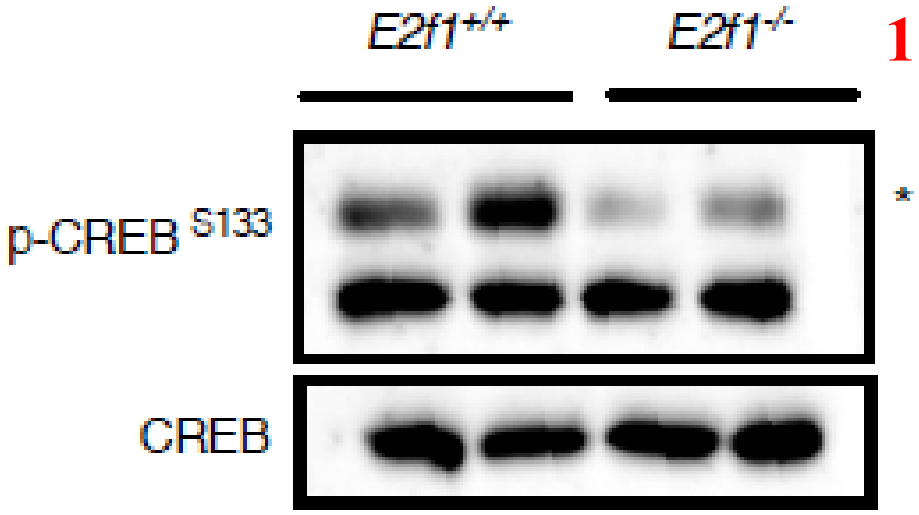




3.2 CREB phosphorylation

cAMP/PKA 途径中，胰高血糖素处理后，cAMP升高导致PKA激活，从而使丝氨酸133上的转录因子CREB磷酸化，磷酸化的CREB通过诱导Pck1及G6PC转录来促进糖异生

1



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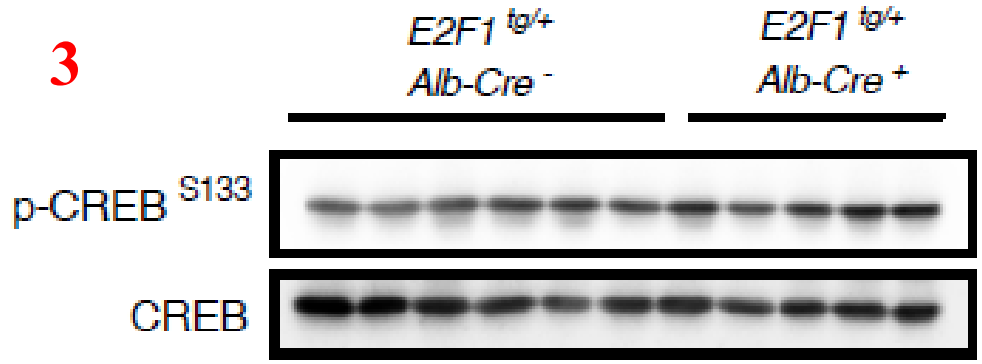
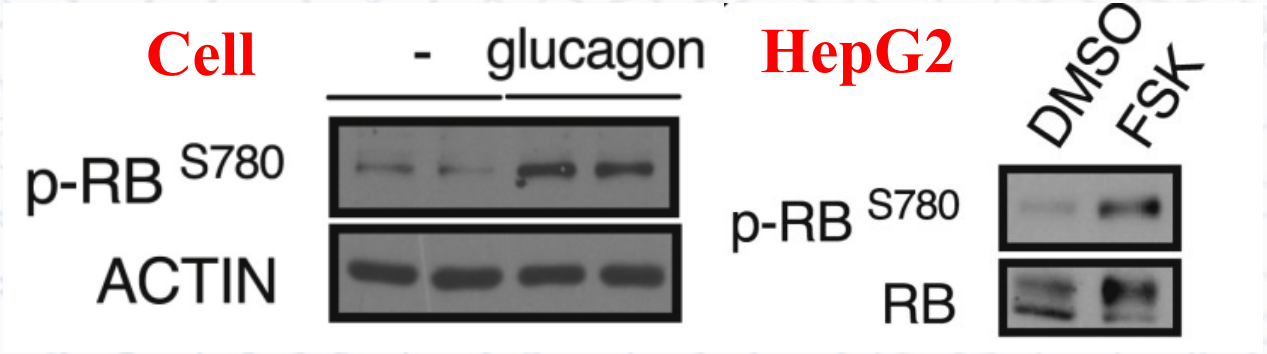
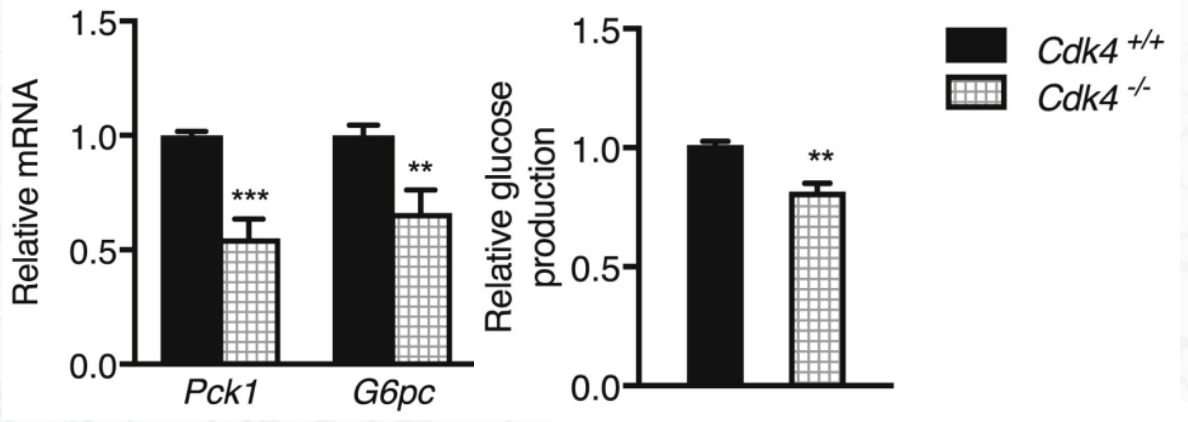
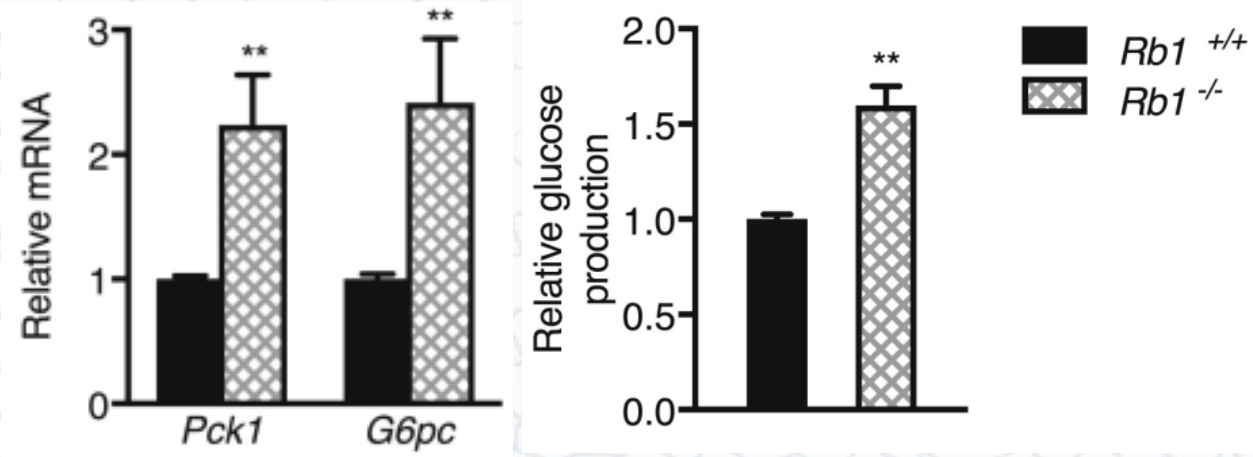
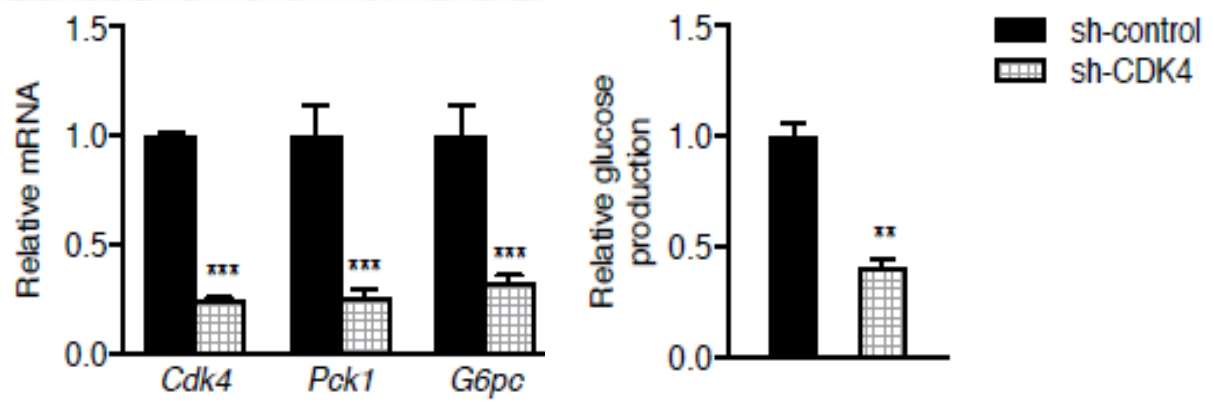


3.3 The CDK4/RB1 pathway participates with E2F1 in the control of gluconeogenesis









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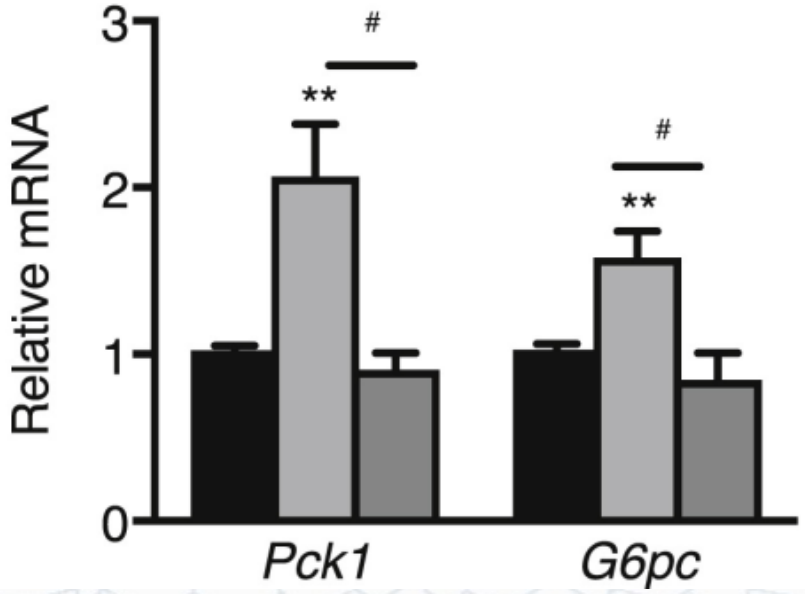
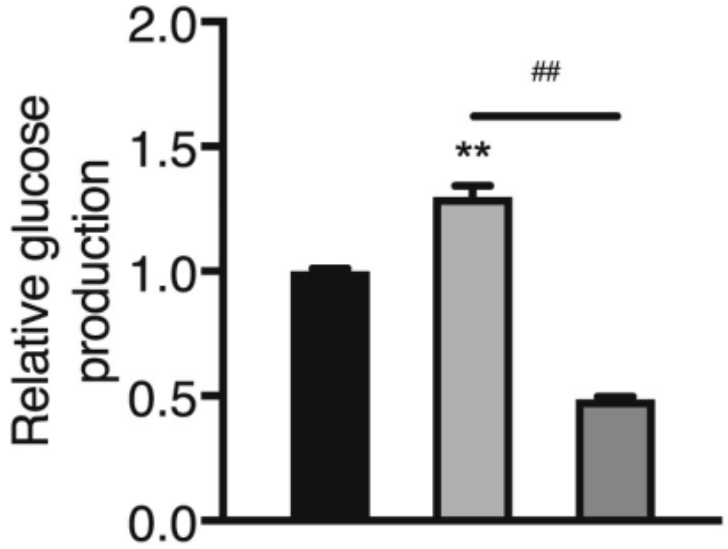
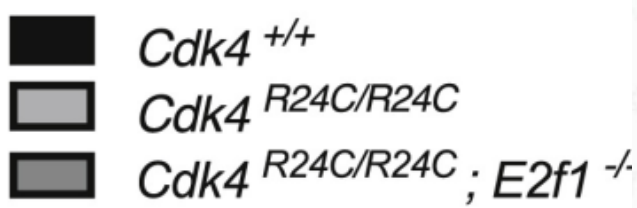






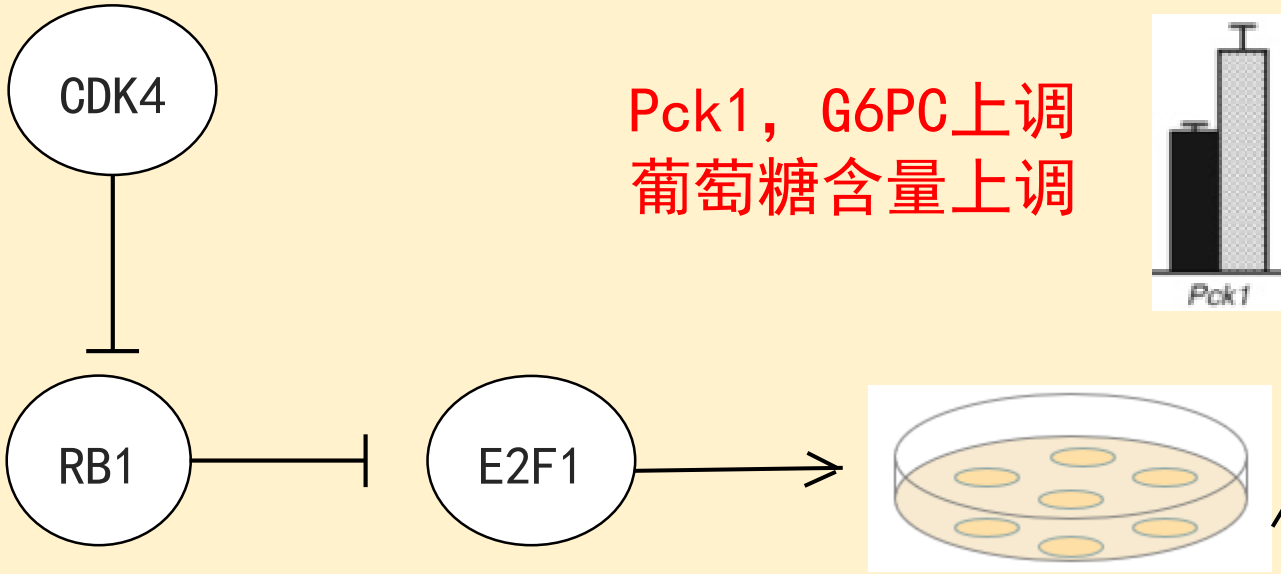
Cdk4 基因插入过表达

E2F1敲除鼠的葡萄糖合成明显减少

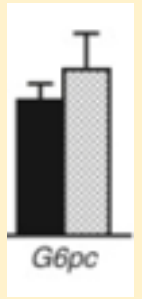
表明cdk4是以依赖E2F1的方式来促进肝糖异生

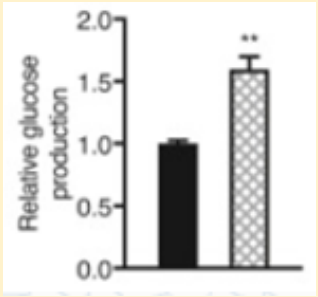
CDK4 / RB1途径与E2F1共同参与肝糖异生的控制

CDK4可以抑制RB1，RB1抑制E2F1，而E2F1促进肝糖异生



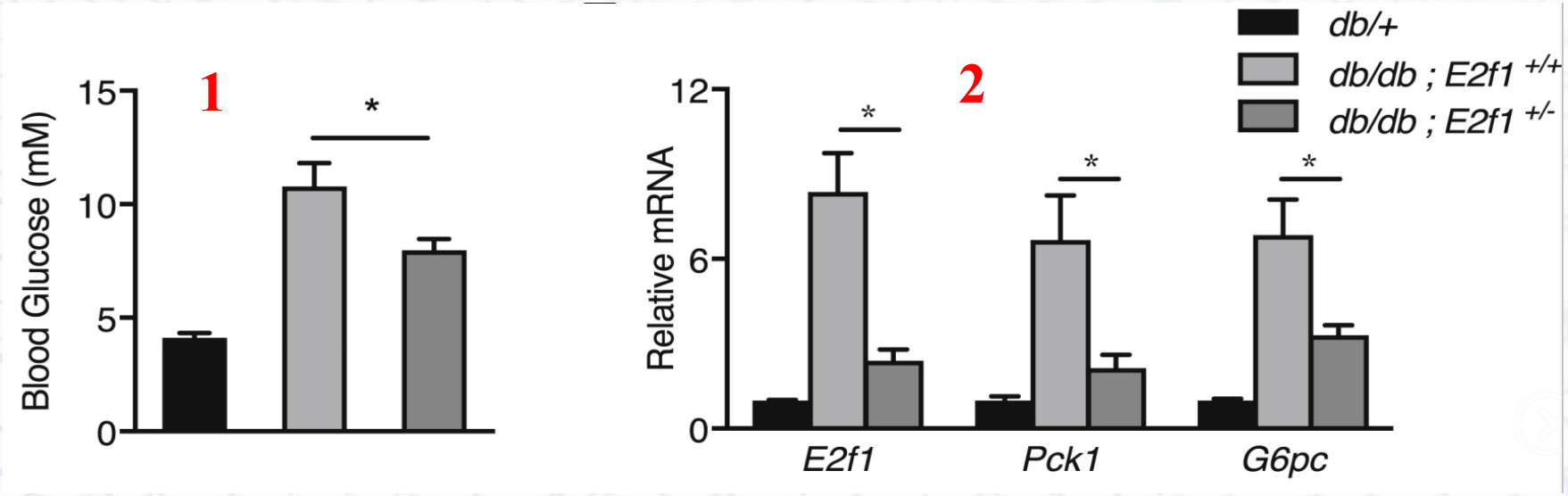
Pck1，G6PC上调
葡萄糖含量上调

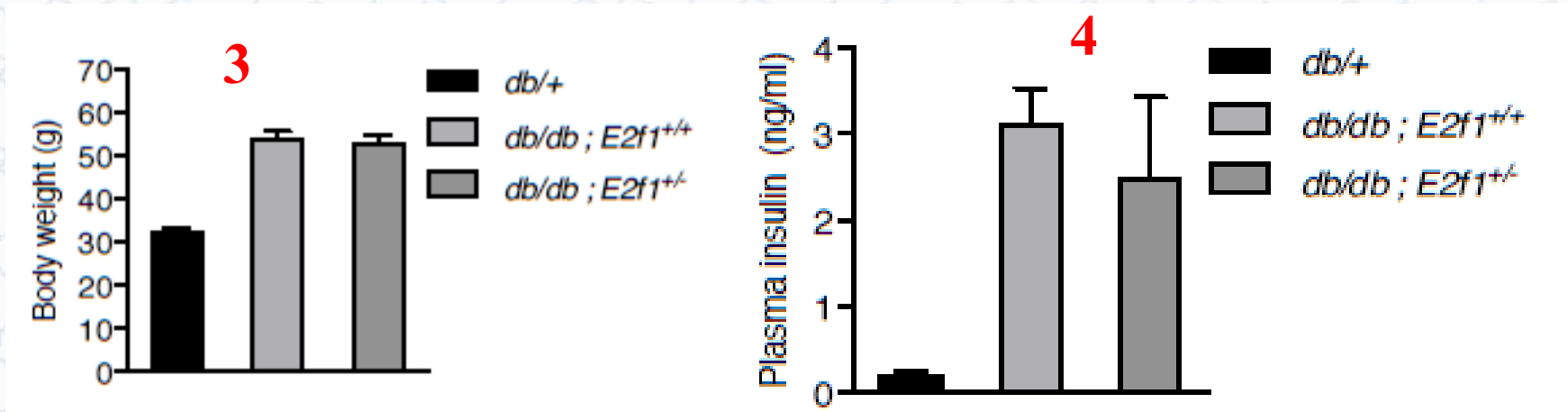




3.4 E2F1 deficiency reduces gluconeogenesis in mouse models of diabetes

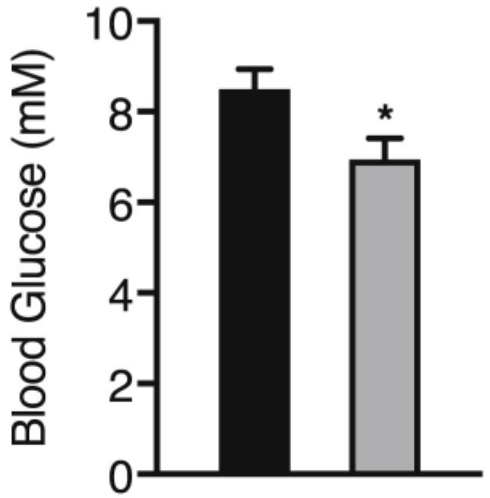
异常的肝糖异生作用是糖尿病患者高血糖的主要原因

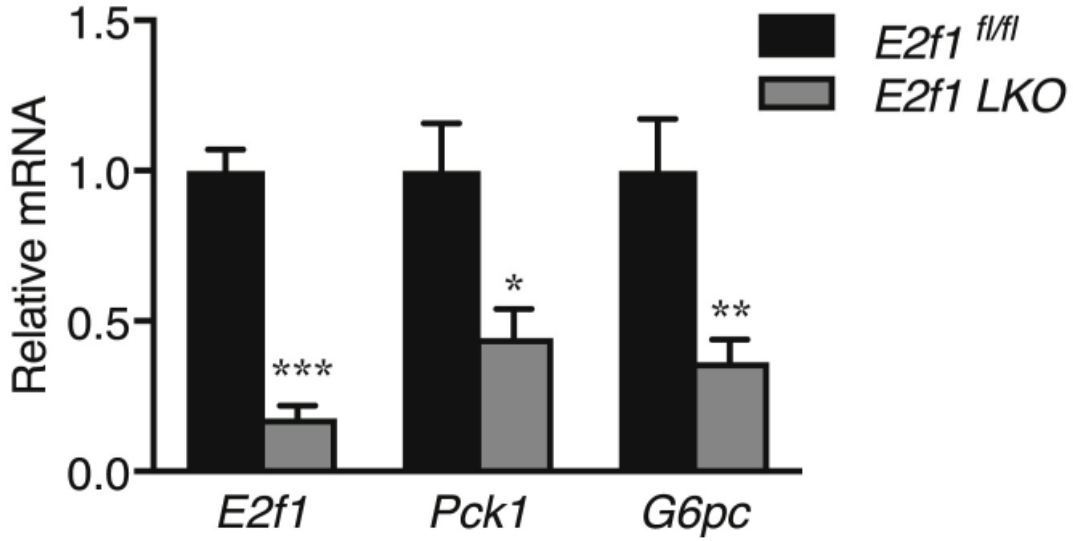


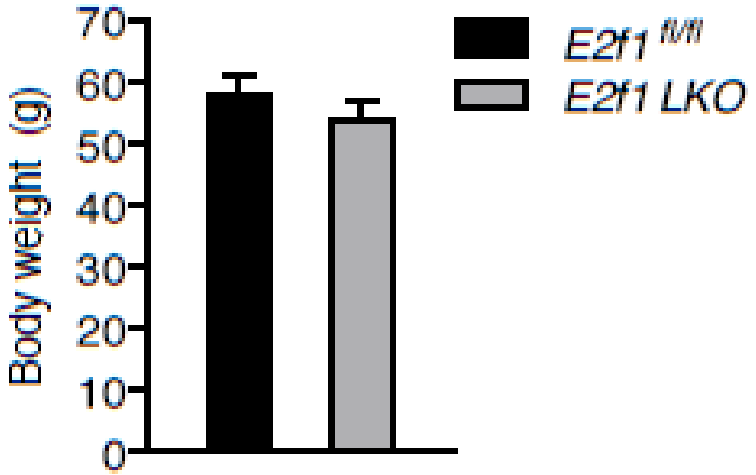


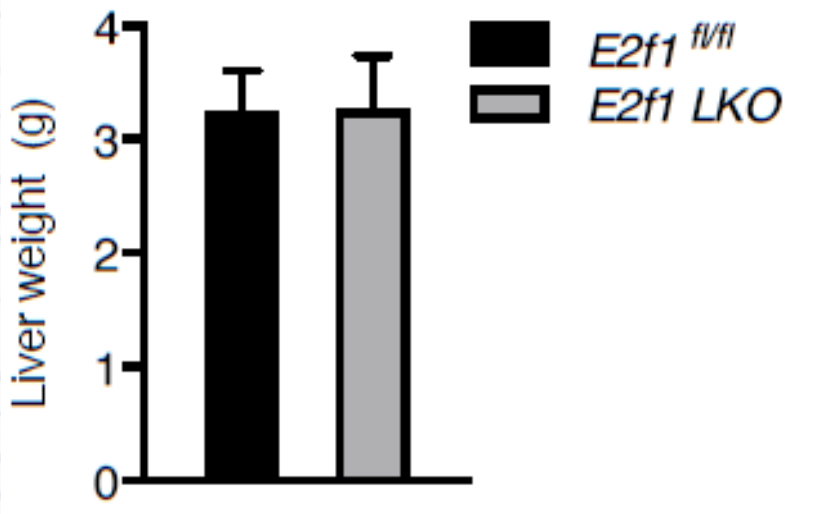
3.4 E2F1 deficiency reduces gluconeogenesis in mouse models of diabetes

HFD
12 weeks









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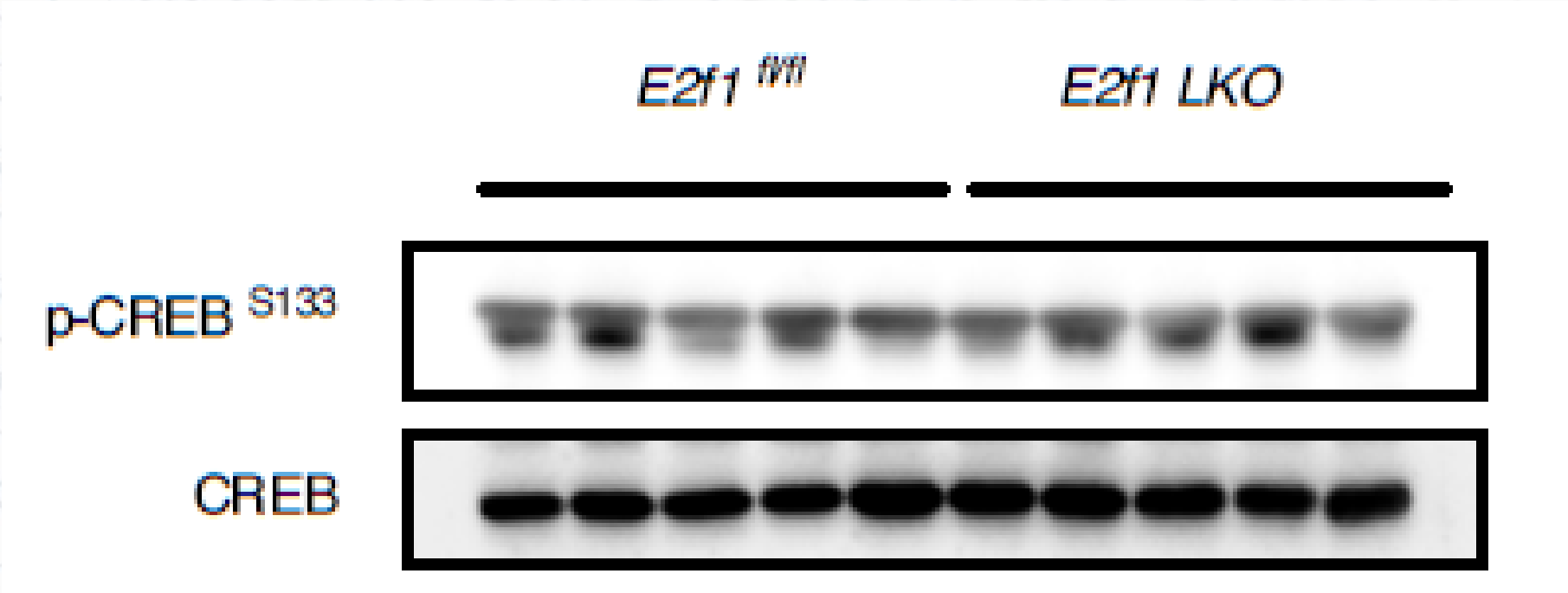
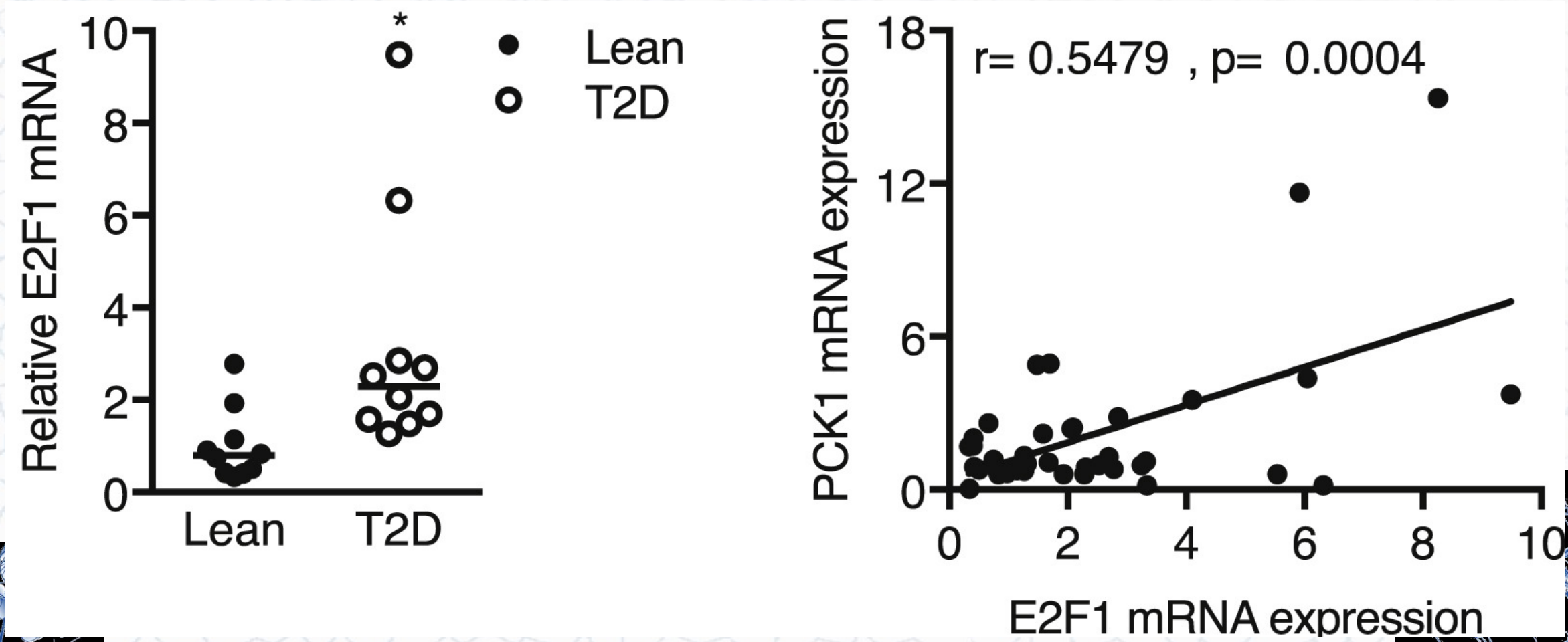


与我们在E2F1 $^{tg/+Alb-Cre+}$小鼠的肝脏中观察到的情况类似，肝糖原异生基因表达的变化不是PKA差异的结果

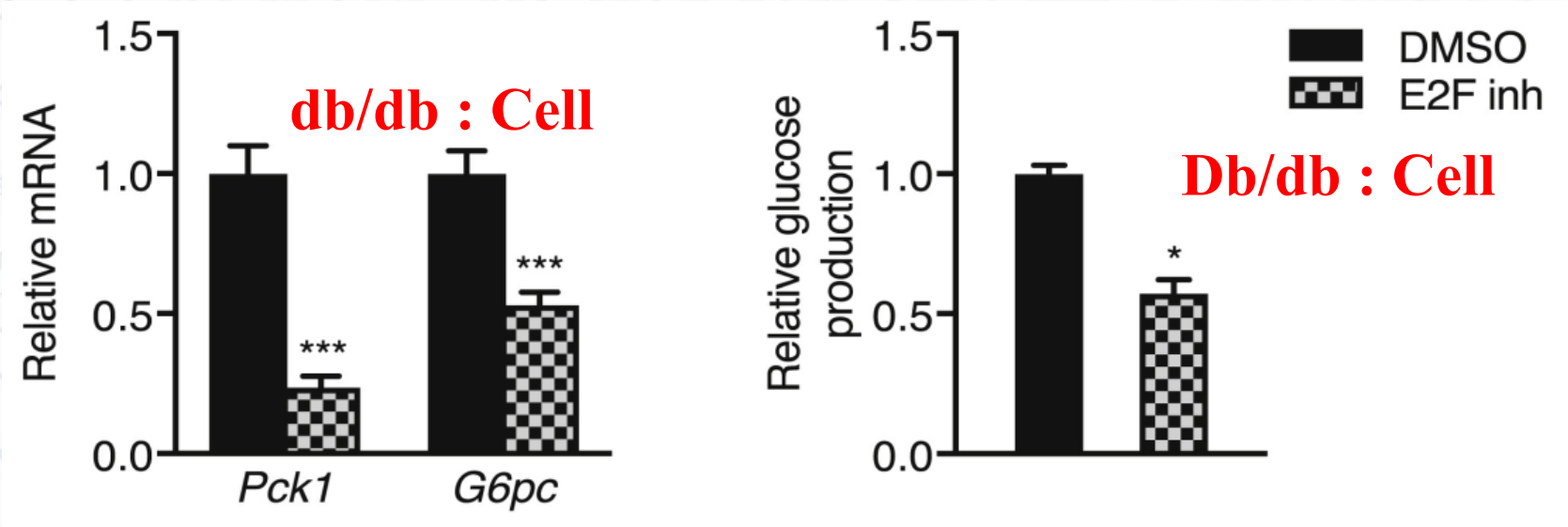
E2F1通过调节肝糖异生而促进肥胖症中的高血糖症

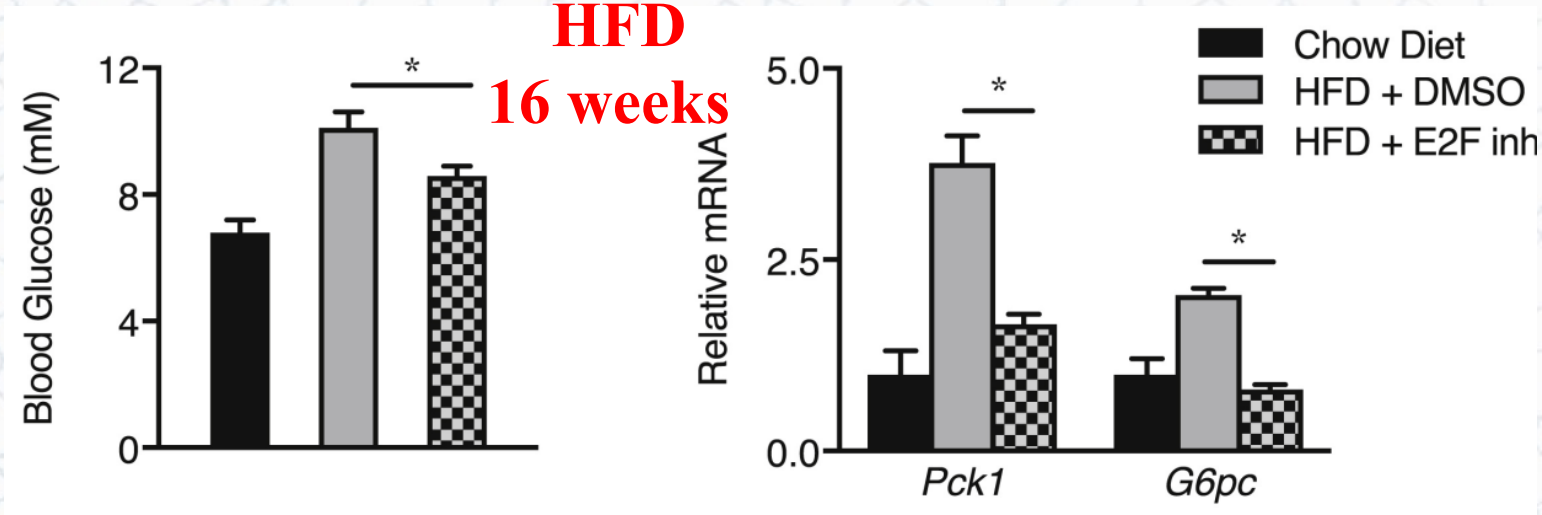
3.5 E2F1 mRNA expression is increased in the livers of diabetic patients and correlates with PCK1 levels

作者试图检查肝E2F1是否也可能导致人体内高血糖　　38 people



3.6 Pharmacological inhibition of E2F1 reduces hyperglycemia in diabetic mice





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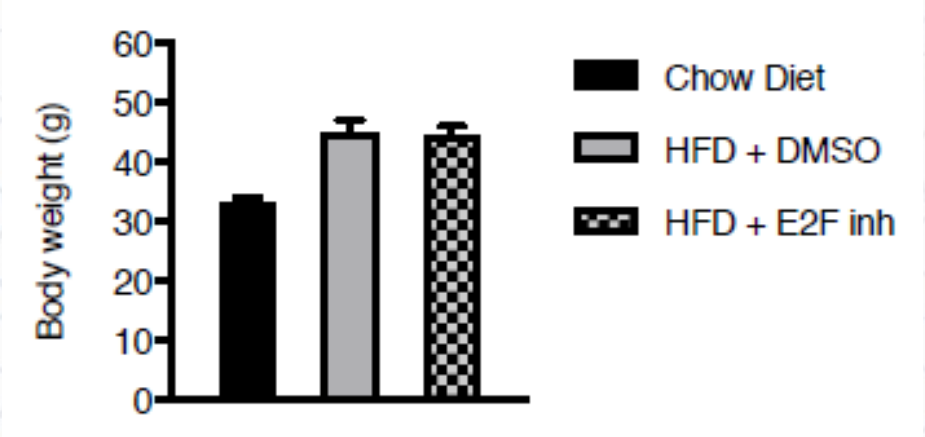

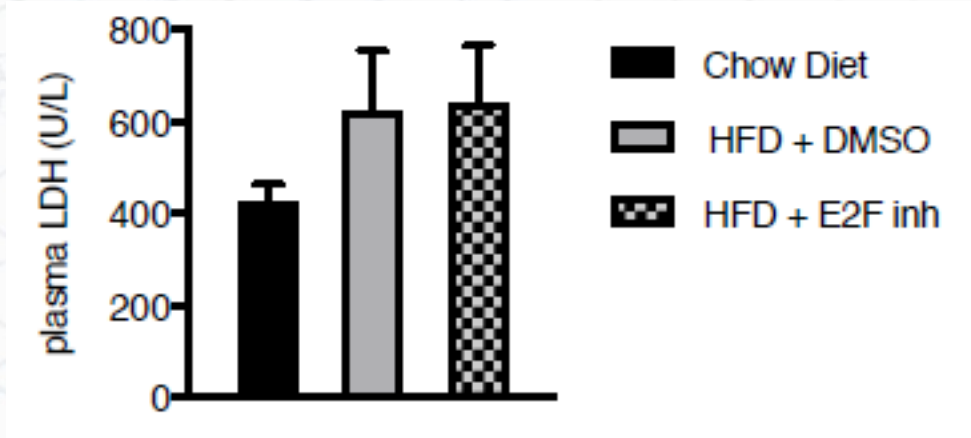

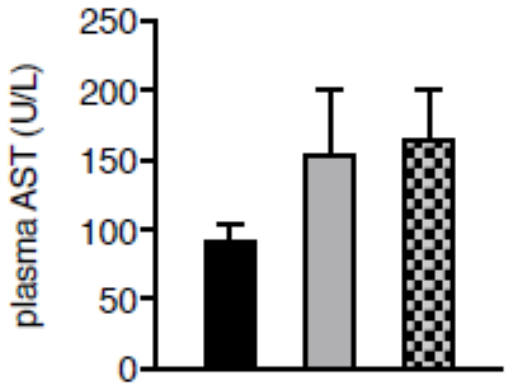

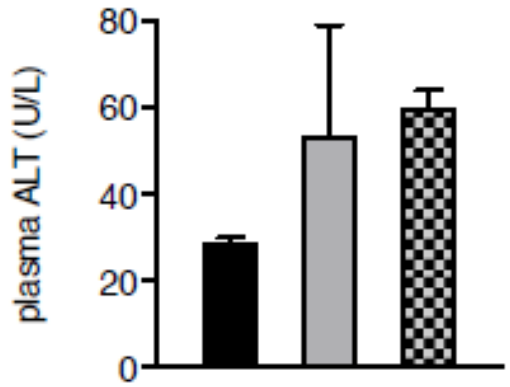

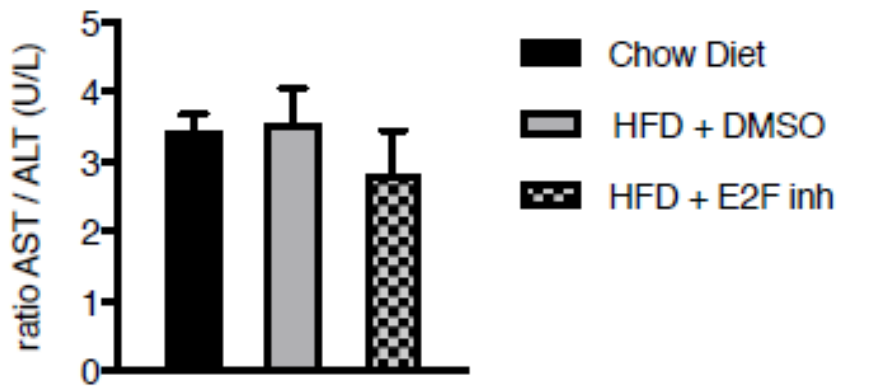

该治疗对小鼠体重、乳酸脱氢酶和转氨酶ALT和AST的循环水平均无影响，证明没有肝毒性

肆

内容总结与启发

4 内容与启发

内容总结

作者证明该转录因子在胰岛素抵抗期间促进了高脂血症和高血糖症。

肝细胞中CDK4-RB1-E2F1途径导致糖原异生基因表达和葡萄糖生成的变化。

作者使用基因敲除、过表达找出E2F1在肝细胞中的作用，排除PKA途径作用接着，通过E2F1与PCK1之间的相关关系找出作用途径。

验证E2F1的作用并回到人类中证实，并在糖尿病新治疗。

4 内容与启发

启发

1、了解到除了整体敲除之外还有特定组织敲除的技术。

2、初步了解了染色质免疫。

3、学习到了作者对信号通路研究的方法。

感谢聆听，请各位老师
同学批评指正！